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EXAMINER
KEMMERER, E

ART UNIT	PAPER NUMBER
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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to PRELIMINARY communication filed on 3/27/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-4, 9, & 24-33 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☑ Claims 5-8, & 10-23 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☑ Claims 1-4, 9, & 24-33 are rejected.

5. ☐ Claims _____ are objected to.

6. ☑ Claims 1-23 WERE are subject to restriction or election requirement.

7. ☑ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

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EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

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Part III DETAILED ACTION

Introduction

The instant application is a file wrapper continuation of application 08/086427, now abandoned. Prosecution continues as from the parent.

Withdrawn Objections and/or Rejections

The requirement to review the application for typographical errors as set forth at p. 2 of the previous Office Action (Paper No. 8, 26 July 1994) is withdrawn in view of the amendments correcting same (Paper No. 14, 30 January 1995).

The objection to the specification under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure and the corresponding rejection of claim 4 as set forth at pp. 2-3 of the previous Office Action (Paper No. 8, 26 July 1994) is withdrawn in part upon further consideration of Figure 4 and Applicant's discussion thereof (Paper No. 14, 30 January 1995). However, claim 4 is now included in the scope rejection previously applied to claims 1-3 and 9. Please see section on 35 U.S.C. § 112, first paragraph, below.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 9, and 24-33 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to $KGF_{des1-23}$ as set forth at pp. 4-5 of the previous Office Action (Paper No. 8, 26 July 1994). See M.P.E.P. §§ 706.03(n) and 706.03(z).

Applicant argues (pp. 12-17, Paper No. 14, 30 January 1995) that the rejection has been obviated by the amendments to the claims removing the phrase "or an analog thereof", such that only $KGF_{des1-23}$ is encompassed by claims 1-4 and 9. Applicant also urges that the specification teaches the skilled artisan how to make and use the $KGF_{des1-23}$ fragment, as well as analogs thereof without undue experimentation. Specifically, Applicant urges that the scope of the claims bears a reasonable correlation with the scope of enablement provided by the specification, that no undue experimentation would have been required to evaluate the claimed KGF fragments, and that working examples are not required to establish enablement. Applicant also urges that it is generally accepted in the art that conservative amino acid replacements would not substantially affect a protein's properties. Applicant points to the claims' requirement (and the specification's definitions) that the KGF fragments and analogs retain activity. Finally, Applicant concludes that no undue experimentation would have been required to make and use the claimed invention, and points to case law as supporting enablement for conservatively substituted proteins in general. Applicant's arguments have been fully considered but are not deemed to be persuasive for the following reasons.

Contrary to Applicant's characterization, claims 1-4 and 9 are not limited to $KGF_{des1-23}$ due to the open claim language used in claim 1. Structurally, claim 1 encompasses numerous KGF fragments such as, for example, the single amino acid 24 of mature KGF, KGF fragments lacking both N-terminal and C-terminal amino acids, KGF fragments lacking N-terminal and central amino acids, and KGF fragments lacking the first 23 amino acids and containing alterations in the remaining structure. Additionally, it is not clear which portion of the claimed KGF fragment must be identical to mature, full-length, native KGF. Thus, claims 1-4 and 9 encompass $KGF_{des1-23}$ but is not limited to same. Similarly, claim 24 recites open claim language. More critical for claims 24-33, however, is the fact that the amino acid numbering system of SEQ ID NO: 1 and Figure 1 are not in agreement, and thus it is not clear which fragments are encompassed by the claims (see section on 35 U.S.C. § 112, second paragraph, below for a more detailed discussion of this issue). Therefore, claims 24-33 are not limited to $KGF_{des1-23}$ and its analogs, as characterized by Applicant. Therefore, the arguments pertaining to $KGF_{des1-23}$ do not support enablement for the full scope of the claims. Also, since the actual scope of the claims is much broader than that characterized in Applicant's arguments, it is maintained that the scope of enablement provided by the specification does not correlate reasonably with the scope of protection sought by the claims.

Furthermore, the Examiner maintains that fragments and analogs of KGF other than $KGF_{des1-23}$ are not enabled by the specification in view of the literature providing evidence of the unpredictability of KGF fragment activity, and of conservatively substituted proteins generally.

For example, Ron et al. (CC of record) discloses KGF fragments lacking N-terminal amino acid sequences both shorter and longer than the 23 amino acid sequence deleted in $KGF_{des1-23}$, and all of the fragments displayed decreased mitogenic activity. This evidence also distinguishes the instant fact pattern from that of the case law cited by Applicant as supporting enablement of conservatively substituted proteins in general. Evidence can also be found in the art that conservative amino acid substitutions often result in loss of activity in a variety of proteins. Since the specification provides no guidance as to which amino acid residues of KGF can be substituted without affecting activity, claiming analogs of KGF is tantamount to an invitation to the skilled artisan to use the current invention ($KGF_{des1-23}$) as a starting point for further experimentation. Simply requiring in the claims and in the definitions provided by the specification that the resulting fragments and analogs of KGF must retain activity does not in itself provide guidance to the skilled artisan regarding which of the many KGF fragments and analogs could be constructed which would be expected to retain activity, without practicing undue experimentation. In effect, the skilled artisan is asked to attempt to predict functional characteristics from mere sequence data. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's

structure/function relationship, e.g. such as various sites or regions directly involved in receptor binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science, Vol. 247, pp. 1306-1310, especially p.1306, column 2, paragraph 2). Even if the receptor-binding and active site residues of KGF were identified in the specification, this would not be sufficient, as the ordinary artisan would immediately recognize that receptor-binding and active sites must assume the proper three-dimensional configuration to be functional, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. Additionally, receptor-binding activity is a feature of both agonists (muteins having biological activity) and antagonists (muteins having little or no biological activity). Mutations in the receptor-binding site can also result in muteins having biological activity but reduced receptor-binding capability. In the absence of any guidance regarding which of these possible muteins or analogs would possess the desired characteristics envisioned by Applicant's invention, the reliance on receptor binding alone is insufficient to enable the breadth of the claims. Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in KGF or $KGF_{des1-23}$ which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made therein. See Ex parte Forman, 230 U.S.P.Q. 546 (BPAI 1986) with regard to the issue raised above. It is deemed that to make each of the possible

amino acid replacements for each of the non-essential residues, even if only conservative replacements were made, would constitute undue experimentation.

35 U.S.C. § 112, Second Paragraph

Claims 24-33 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Since SEQ ID NO: 1 and Figure 1 do not have the same amino acid numbering system, it is not clear which KGF fragments are being claimed. When one refers to SEQ ID NO: 1, a KGF fragment consisting of residues 55 to 194 is the same as $KGF_{des1-23}$. When one refers to Figure 1, a KGF fragment consisting of residues 55 to 194 makes no sense, since the protein ends at residue 163. Furthermore, it is not clear what is meant by a sequence "corresponding to" another sequence. This could be interpreted by the skilled artisan as being either identical to or merely similar to. Since the claimed sequences are not clearly defined, the metes and bounds of the claimed invention cannot be determined, and the claims fail to comply with 35 U.S.C. § 112, second paragraph.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Elizabeth C. Kemmerer, whose telephone number is (703) 308-2673. The

Examiner can normally be reached on Tuesdays through Fridays from 7:30 a.m. to 5:00 p.m. The Examiner can also be reached on alternate Mondays.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Garnette D. Draper, can be reached on (703) 308-4232. The fax number for this Art Unit is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist whose telephone number is (703) 308-0196.

GARNETTE D. DRAPER
SUPERVISORY PRIMARY EXAMINER
GROUP 1800

Elizabeth C. Kemmerer, Ph.D.
November 28, 1995